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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,283	09/08/2000	C Alexander Turner Jr	LEX-0041-USA	3550

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 01/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/658,283	TURNER JR ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this c mmunicati n appears on the cover sheet with the c rrespondenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1,2 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-2, 6-9 are pending and under consideration.

Response to Amendment

Applicant's arguments filed 10/12/2004 have been fully considered but they are not persuasive. For the reasons set forth below.

New and remaining issues are set forth below

Claim Rejections - 35 USC §§ 101, 112 first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims as written read on host cells, including eukaryotic and animal cells. There is no limitation wherein the host cells are isolated or in culture, therefore the claims read on transfected cells in a human, and thus are not patentable subject matter. This rejection could be obviating by adding a limitation wherein the host cells are isolated or in culture.

Claims 1-2, 6-9 stand rejected, under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility, for reasons of record set forth the Office action sent 7/1/2002, 12/26/2002 and 4/6/2004. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

First, the key issue at dispute is not a matter of whether the present nucleic acids encode GPCRs; rather, it is a matter of whether the present nucleic acids encode GPCRs with defined biological functions; it is a matter of whether the present nucleic acid sequences have a patentable utility. The annotations for the published sequence in Genbank are based upon sequence homology and there is no sufficient information which defines unambigously the functions of the published sequences.

The claimed nucleotide sequence shares 93% percent identity at the amino acid level with a sequence present in GenBank which has been annotated as VIGR GPCR mRNA (GenBank, Accession No. AAO13250). This has been fully considered but is not deemed to be persuasive because (i) the annotation for the published sequence in Genbank is, again, based upon sequence homology and there is no sufficient and credible information that indicates the published sequence is a truly functional GPCR; and (ii) even if the cDNA encodes a functional GPCR, the sequence similarity does not render the sequence of the present invention a specific function and a patentable utility because there is no single well-established utility for the GPCR family due to

the great diversity in structures and functions of the GPCR family and the functions of a GPCR has to be determined experimentally as noted immediately above.

Secondly, the art teaches that it is impossible to predict precisely the functions of protein molecules solely base upon sequence analysis, in view of the diversity of structure and functions of GPCRs (Bork and Eugene V. Koonin, Nature Genetics 18:313-318,1998). There were nearly 2000 GPCRs up to 1998 and they are classified into over 100 subfamilies according to sequence homology, ligand structure, and receptor function. There are putative seven transmembrane molecules, which do not appear to be coupled to a G protein (Ji et al., J. Biol. Chem. 273:17299-17302, 1998; see beginning of the article). A variety of studies have shown that minor differences in sequence can account for different binding affinities and activities. For example, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Science 290: 523-527, 2000).

Even if the encoded proteins are found to be a G-protein coupled receptors, they are orphan receptors. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the protein of SEQ ID NO: 2, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. Stadel et al. (Stadel et al. Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery. TIPS Vol. 18: 430-437, 1997) teaches that the initial challenge is to determine the function of each orphan receptor through the identification of activating ligands and, once the function is clarified, link the orphan receptor to a specific disease and thus establish it as a candidate for a comprehensive drug discovery effort (page 433,

column 1, first paragraph). Thus Stadel et al. teaches that before an orphan GPCR has a use, the activating ligand must be determined. Thus, without a known ligand, orphan receptors do not have a well-established, specific or substantial utility. Stadel et al. teaches that characterized GPCR's are attractive therapeutic targets, and that orphan receptors may have a similar potential, but that their activating ligand must first be determined (page 433, column 1, first paragraph).

The fact pattern of the claimed invention is similar to that of Example 12 of the utility Guidelines, in that the claimed nucleic encodes a receptor with no known biological activity, other than that it is a GPCR, moreover, unlike the receptor in Example 12, there is no known binding partner for the claimed receptor. Example 12, concludes that the receptor in the Example has no well established utility since there is no evidence at points to a property for the receptor and that there is no art of record that points to an activity for said receptor. In the instant case, the fact that the claimed invention allegedly encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific ligand for each receptor is known, unless the biological activity of the receptor is disclosed and unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility. As has been shown, in order for a GPCR to have a well-established, or specific and substantial, utility, the activating ligand must be known, thus the fact pattern is more like Example 12.

Furthermore, there is no single well-established utility for the GPCR family due to the great diversity in structures and functions of the GPCR family. Even for a subfamily of the GPCR, the structure and biological activities may vary broadly. The functions of a GPCR has to

be determined experimentally. Therefore, even the sequence analysis can place a GPCR into the GPCR family; such an assignment does not render a specific biological function and thus a well-established utility to the GPCR, as is the case here.

According to MPEP § 2107, a rejection for lack of utility is imposed when an invention lacks an asserted specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. In the instant case, the preponderance of the evidence indicates that a person of ordinary skill in the art would not immediately appreciate why the invention is useful based on the characteristics of the invention, for the reasons set forth above, and further, that the claimed invention lacks a specific or substantial utility. Thus the *prima facie* showing of no utility has been made.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a complement of a nucleic acid which hybridizes to a nucleic acid encoding SEQ ID NO: 2, or a nucleic acid which hybridizes to a complement of a nucleic acid of SEQ ID NO: 1. The claims thus encompass variants of nucleic acids. However, Applicants do not disclose any actual or prophetic examples on expected performance

parameters of any of the possible variants of SEQ ID NO: 2. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, As an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass nucleic acids

encoding variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. While the Specification discloses that the encoded polypeptide functions in the chondrocyte re-differentiation assay, the claims do not set forth a functional limitation for the nucleic acids encoding the variant polypeptides and since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for nucleic acids encoding polypeptide variants of SEQ ID NO: 2, and has not taught how to make nucleic acids encoding

polypeptide variants of SEQID NO: 2, it would require undue experimentation of one of skill in the art to make and use the claimed polynucleotides.

Claim 2 is rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a complement of a nucleic acid which hybridizes to a nucleic acid encoding SEQ ID NO: 2, or a nucleic acid which hybridizes to a complement of a nucleic acid of SEQ ID NO: 1. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded polypeptide. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 encoding SEQ ID NO: 2 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 7, 9 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 1, does not reasonably provide enablement for in vivo transfection, for reasons of record set forth in the Office Action of 4/6/2004.

The specification on page 25 discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, including cells within a host animal. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 1 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, the claims as written are not enabled. This rejection could be overcome by addition of the limitation wherein the host cells are isolated.

Applicant argues that the submitted reference is directed not at the claimed invention, but a process in which the claimed invention might be used, thus this reference cannot reasonably be used to support a prima facia case against the presently claimed invention. For the record, though irrelevant to the instant case, gene therapy has been successful in some cases. However, All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled (MPEP 2164.08). The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without `undue experimentation'." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Here, the claims encompass nucleic acids of the current invention expressed in a wide variety of host cell types, including cells within a host animal, and also including humans. The Eck & Wilson reference establishes that the making or use of a host cell in an animal or human is unpredictable, and is not routine. Applicant further argues that the rejection is irrelevant, because the claims of the present invention are not directed at gene therapy or the use of a host cell. The claims of the present invention are directed at a host cell comprising a particular vector. However, according to 112 first paragraph, the claims must be enabled for the making and use of a claimed invention. Applicant further argues that it must be noted that claims direct at a host cell have been allowed in hundreds of patents which contain no more disclosure than the present case, however, each application is examined on its own merits, and here the claims as written are not enabled.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Art Unit 1646
January 4, 2005

JOSEPH MURPHY
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